New claim 22 is supported by the sentence bridging pages 11-12. New claim 23 is supported by original claim 14. New claim 24 is supported at page 11, line 25. New claim 25 is supported at page 16, line 26. New claim 26 is supported as described above and furthermore at page 5, lines 12-18. New claim 27 is supported at page 4, lines 26 and 30. New claim 28 corresponds to new claim 18 discussed above. New claim 29 is supported at page 1, lines 35-37. New claim 30 is supported as discussed above with respect to new claim 20. New claims 31-35 correspond to claims 21-25 discussed above. New claim 36 is supported for example in the paragraph bridging pages 11-12. New claim 37 is supported at page 12, lines 7-16. New claim 38 is supported by examples 1 and 2. New claims 39-46 correspond to claims discussed above. Claims 47-50 are supported on pages 6-8. Claims 51 and 52 are supported as discussed above. Claim 53 is supported on page 11, lines 26-29. New claim 54 is supported on pages 1-3 and 14-15. New claim 55 is supported by pages 1-3 and examples 2 and 4. New claim 56 is supported for example at page 6, lines 6-15. New claim 57 is supported for example from page 4, line 19 to page 6, line 15, particularly page 5, lines 32-35. New claim 58 is supported as claim 57, particularly at page 5, line 35 to page 8, line 35. New claim 59 is supported on pages 4-8. New claim 60 is supported as discussed with respect to claim 59 and furthermore at page 9, lines 14-21. New claim 61 is supported as discussed above. New claims 62-64 are supported at page 21,

lines 24-27 and pages 27-29. New claims 65-67 are supported at page 16, lines 3-23. New claims 68-70 are supported as discussed above. New claim 71 is supported in the paragraph bridging pages 12-13. New claim 72 is supported on page 14, lines 9-28. New claim 73 is supported in the paragraph bridging pages 14-15. New claim 74 is supported on page 15 and by example 3. New claims 75-78 are supported as discussed above. New claim 79 is supported on page 15, lines 19-23. New claim 80 is supported on page 15, lines 24-26. New claim 81 is supported on pages 6-8, particularly page 7 at lines 24-26. New claim 82 is supported at page 11, lines 27-29. New claim 83 is supported at page 11, lines 29-35. New claim 84 is supported at page 13, lines 5-9. New claim 85 is supported at page 13, lines 9-10 and page 29, line 1. New claim 86 is supported at page 15, lines 5-9. New claim 87 is supported at page 13, lines 9-10 and page 29, line 1. New claim 88 is supported at page 13, lines 6-10 and page 29, line 1. New claim 89 is supported at page 14, lines 1-8. New claim 90 is supported at page 14, lines 9-10. New claim 91 is supported at page 14, lines 22-34. New claim 92 is supported at page 15, lines 15-17. New claim 93 is supported at page 15, lines 17-19. New claim 94 is supported at page 16, line 12. New claim 95 is supported at page 8, line 2 and page 19, line 14. New claim 96 is supported at page 19, line 30 to page 20, line 11. New claim 97 is supported at page 12, lines 23-27. New claim 98 is supported at page 22, line 33-35. New claim 99 is

supported at page 22, line 35 to page 23, line 3. New claim 100 is supported at page 22, line 35 to page 23, line 3. New claim 101 is supported at page 27, lines 9-17. New claim 102 is supported at page 27, lines 22-24. New claim 103 is supported at page 28, line 8. New claim 104 is supported at page 29, lines 3-5. New claim 105 is supported at page 29, lines 6-12. New claim 106 is supported at page 8. Support for the remainder of the claims is believed to be apparent from the foregoing descriptions.

The following discussion now sets forth a brief summary of the features of the present invention set forth in the new claims which are patentably distinct and nonobvious over the prior art.

Generally, the present invention provides novel arrays and methods for analyzing polynucleotide sequences.

At the time of the invention, such arrays and methods for analyzing polynucleotide sequences did not exist. Early workers in the field had used allele specific 19 mers in a conventional blotting format: the target was bound to a permeable membrane; the oligonucleotides were labelled, dissolved probes. Dattagupta (EPA 235 726) adapted this system by immobilizing the same 19 base sequences on a membrane and hybridising with labelled target DNA. This was the first patent description of a "reverse dot-blot". Clearly there are a number of problems in blotting oligonucleotides. Adsorption to the membrane is very

inefficient and variable; the absorption process involves some of the bases, which become unavailable for Watson-Crick pairing. Some of these problems could have been overcome by linking the oligonucleotides to the membrane covalently, but the only methods for covalent attachment available in the art for linkage of preformed oligonucleotides to membranes also involved the bases. Instead Dattagupta ameliorated the problem of inefficient linkage and of sequestration of the bases, by extending the oligonucleotides with arbitrary sequence, and by ligating them into polymers, hardly methods that could be adapted to routine use, or to large-scale arrays.

A further problem of using oligonucleotides in the reverse dot-blot is that the pores of the membranes used for blotting are very small, typically ca. 0.45 μm. Small oligonucleotides can readily diffuse into these pores and attach below the surface. But the larger targets cannot, so that most of the oligonucleotide molecules are unavailable for hybridisation.

Finally, solution spotted onto porous membranes diffuses. The spot has an arbitrary size and shape, making accurate analysis difficult if not impossible.

Nevertheless, "blotting" was the state of the art at the time of the instant invention and Dattagupta adapted it as best he could to oligonucleotides. The inadequacies are well illustrated by the poor quality of his data.

It was appreciated by Professor Southern (who had developed the first blotting methods in the early 1970's) that in order to bring out the full potential offered by oligonucleotide arrays something other than blotting was needed. Professor Southern was the first to conceive and prove that the shortcomings of blotting could be circumvented by several new features: oligonucleotide attachment should be covalent; it should be at one end of the oligonucleotide; it should be on the surface of the support, which should be impermeable; it should be confined to well defined regions of the surface; it should preferably allow for the fabrication of arrays comprising large numbers of oligonucleotides in a small area. Nothing in the art suggested these innovative features and implementation needed a number of inventive steps.

Taken together, it can be seen that these innovations, all of which are disclosed in the instant specification, open up many application which were previously not possible. Some are illustrated by comparing the analysis of the β-globin gene in Dattagupta patent with the analysis of the same locus in the instant application. In the Dattagupta patent, an elaborate procedure is used to create an array of oligonucleotides by blotting; there is no discrimination between the two alleles (Examples 6 and 7). In the instant application, a simple procedure is used to make an array of three alleles in which each is represented as a set with varying length and sequence; this